Pulmonary Hypertension and Cardiac Anesthesia: Anesthesiologist's Perspective

Abstract

Perioperative management of pulmonary hypertension remains one of the most challenging scenarios during cardiac surgery. It is associated with high morbidity and mortality due to right ventricular failure, arrhythmias, myocardial ischemia, and intractable hypoxia. Therefore, this review article is intended toward the anesthetic considerations in the perioperative period, with particular emphasis on the selection of technique and choice of anesthesia with maintenance, anesthetic drugs, and the recent intraoperative recommendations for prevention and treatment of pulmonary hypertensive crisis.

Keywords: *Anesthesia, pulmonary hypertension crisis, pulmonary hypertension*

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Introduction

Cardiac anesthesiologists routinely encounter pulmonary hypertension (PH) in the perioperative period. Anesthesia administration in this subset of patients is a challenging task due to hyperreactive airway and risk of right ventricular (RV) failure. However, with the advent of innovative treatments and advanced hemodynamic monitoring, successful management of these patients is a reality nowadays. The functional status and life expectancy of patients with this condition have significantly increased; so, these patients are likely to encounter noncardiac surgical procedures too. The anesthetic management of such patients requires a thorough understanding of the etiology, pathophysiology, type, and severity of PH along with the nature of the surgical procedure.

Definition

According to the Fourth World Symposium, PH is defined as "a mean pulmonary artery pressure (mPAP) >25 mmHg at rest, and more than 30 mmHg during exercise; based on a review demonstrating that the normal mPAP is 14 mmHg."[1] Borderline PH is mPAP between 20 and 24 mmHg.[2]

Etiology and Classification

Recently, original Dana Point classification of PH has been updated[3] and encompasses numerous clinical conditions causing PH [Table 1]. Anesthesiologists usually deal with PH type 2 and 3 in the perioperative period.

Pathophysiology

PH is a conglomeration of various interrelated processes resulting in endothelial dysfunction, vasoconstriction, vascular remodeling with excessive cell proliferation in the presence of reduced cell apoptosis, and thrombosis.

Group 1: Pulmonary arterial hypertension (PAH) results from an excessive vasoconstriction due to abnormal function or expression of potassium channels in the smooth muscle cells and endothelial dysfunction leading to chronically impaired production of vasodilator and antiproliferative agents such as nitric oxide (NO) and prostacyclin, along with overexpression of vasoconstrictor and proliferative substances such as thromboxane A2 and endothelin-1 (ET-1).[3] ET-1 production, which is a potent vasoconstrictor and stimulates smooth muscle cell proliferation, is increased in the pulmonary vasculature.[4]

All forms of PH are believed to result in a state of reduced NO bioavailability which has vasodilatory and antiproliferative properties.[5] Phosphodiesterase-5 (PDE-5) expression is increased in the endothelial smooth muscle cells and right ventricle.[6]

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Table 1: Updated classification of pulmonary hypertension[3]

Type 1

PAH

  Idiopathic

  Hereditary

  Drug and toxin induced

  Associated with

    Connective tissue disease

    HIV infection

    Portal hypertension

    Congenital heart diseases

    Schistosomiasis

  Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

  Persistent PH of the newborn

Type 2

PH due to left heart disease

  Left ventricular systolic dysfunction

  Left ventricular diastolic dysfunction

  Valvular disease

  Congenital/acquired left heart inflow/outflow tract obstruction and cardiomyopathies

Type 3

PH due to lung diseases and/or hypoxia

  Chronic obstructive pulmonary disease

  Interstitial lung disease

  Other pulmonary diseases with mixed restrictive and obstructive pattern

  Sleep-disordered breathing

  Alveolar hypoventilation disorders

  Chronic exposure to high altitude

  Developmental lung diseases

Type 4

Chronic thromboembolic PH

Type 5

PH with unclear multifactorial mechanisms

  Hematological disorders: Chronic hemolytic anemia, myeloproliferative disorders, and splenectomy

  Systemic disorders: Sarcoidosis, pulmonary histiocytosis, and lymphangioleiomyomatosis

  Metabolic disorders: Glycogen storage disease, Gaucher disease, and thyroid disorders

  Others: Tumoral obstruction, fibrosing mediastinitis, chronic renal failure, and segmental PH

PAH: Pulmonary arterial hypertension, PH: Pulmonary hypertension

Genetic cause includes mutation of bone morphogenetic protein (BMP) receptor-2 which leads to loss of inhibitory action of BMP on vascular endothelial and smooth muscle cells growth.[7] Ultimately, chronically elevated afterload results in hypertrophy and dilatation of the right ventricle, and a metabolic shift from oxidative mitochondrial metabolism to the glycolytic pathway, which is related to cardiac ischemia[8] and progressive right-sided heart failure

with decreased cardiac output and the typical clinical symptoms occur [Table 2].[9,10]

Group 2: PH due to left heart disease triggers "back pressure" effects in the pulmonary veins, and consequently, an elevation in pulmonary artery pressure occurs. This causes reactive changes in the pulmonary vascular bed, accompanied by vasoconstriction, remodeling, and increase in the transpulmonary pressure gradient (TPG = mPAP − pulmonary capillary wedge pressure [PCWP]).[11] In these cases, pulmonary vascular resistance (PVR) is within normal range.

Group 3: This involves hypoxic vasoconstriction, mechanical stress of hyperinflated lungs, loss of capillaries, inflammation, and toxic effects of smoking. There are also data supporting an endothelium-derived vasoconstrictor–vasodilator imbalance.[3]

Group 4: PH occurs due to nonresolution of acute embolic masses that undergo fibrosis leading to mechanical obstruction of pulmonary arteries and pulmonary vascular remodeling results. Thrombophilic factors, such as antiphospholipid antibodies, lupus anticoagulant, and elevated factor VIII, have been statistically associated with chronic thromboembolic pulmonary hypertension, and no abnormalities of fibrinolysis have been consistently demonstrated. Microvascular disease may be related to shear stress in nonobstructed areas, postcapillary remodeling related to bronchial-to-pulmonary venous shunting, inflammation and release of cytokines and vasculotrophic mediators.[3]

Group 5: Pathobiology is unclear or multifactorial.[3]

PH can also be categorized into pre- and post-capillary, and a distinction between two is fundamental in understanding the vascular and hemodynamic changes which are summarized in Table 3.

Treatment

Different treatment modalities as per class of PH are summarized below.[12]

Group 1: Anticoagulation, diuretics, oxygen therapy, and digoxin.

Therapeutic approach is guided by functional status (WHO symptom classification) and objective testing (e.g., 6-min walk test) as follows:
- Low risk, functional Class I–III patients may be treated with oral PDE-5 inhibitors, oral endothelin receptor antagonists (ERAs), or inhaled prostacyclins
- High risk, functional Class III–IV patients should be treated with intravenous (IV) or subcutaneous prostacyclins.

Group 2: They are managed with therapies for left heart failure. The use of pulmonary vasodilators may worsen pulmonary edema by increasing pulmonary blood flow in the presence of elevated left-sided filling pressures. However, few patients have developed intrinsic pulmonary

Table 2: Sign and symptoms of pulmonary hypertension[9,10]

Dyspnea
  Fatigue
  Dizziness
  Dry cough
  Syncope
  Hypoxemia
Prominent "v" waves in jugular pulse with holosystolic murmur, indicating tricuspid regurgitation
Parasternal heave
Hepatomegaly, peripheral edema, and ascites

Table 3: Pulmonary hypertension classification by hemodynamics

Definition	Characteristics (baseline values)	Corresponding WHO group
Precapillary PH	mPAP ≥25 mmHg	All
	mPAP ≥25 mmHg	Group 1
	PAWP ≤15 mmHg	Group 3
	PVR >3 WU	Group 4
	CO normal/reduced/high	Group 5
Postcapillary PH	mPAP ≥25 mmHg	Group 2
	PAWP >15 mmHg	
	CO normal/reduced/high	

PH: Pulmonary hypertension, mPAP: Mean pulmonary arterial pressure, PAWP: Pulmonary artery wedge pressure, PVR: Pulmonary vascular resistance, CO: Cardiac output; high CO can be present in cases of hyperkinetic conditions such as systemic to pulmonary shunts (pulmonary circulation only); anemia; hyperthyroidism; portal hypertension; and sepsis

vascular disease and benefit from pulmonary vasodilator therapy. A small trial suggested potential benefit of PDE-5 inhibitors in patients with heart failure and a preserved ejection fraction if there was a >5 mmHg difference between PA diastolic pressure and PCWP after optimizing volume and blood pressure.

ERAs and prostacyclins should not be used.

Group 3: Management is directed at the underlying lung disease. Pulmonary vasodilators do not have a role and worsens ventilation perfusion (VQ) matching in these patients.

Group 4: PH is potentially curable with pulmonary thromboendarterectomy. There may be a role for pulmonary vasodilators in those who are not surgical candidates.

Group 5: Management is directed at the underlying disease.

Endothelin Receptor Antagonists in Pulmonary Arterial Hypertension

The use of ERAs in PAH management is relatively new, and thus, bosentan, ambrisentan, and recently, macitentan have been approved for use.

Bosentan: It is a dual ERA, which competitively antagonizes the binding of endothelin to both endothelin receptors ET_A and ET_B. The initial oral dose for bosentan therapy is 62.5 mg twice daily for 4 weeks; further, it is increased to a maintenance dose of 125 mg twice daily. Common side effects include liver toxicity and major birth defects. Accordingly, baseline and periodic liver function tests and pregnancy tests are required. Dose adjustments are not required in renal insufficiency. It is a microsomal enzyme inducer and thus reduces the concentration of drugs like warfarin, sildenafil when administered together.[13]

Ambrisentan is a highly selective ET_A receptor antagonist. Dose is 5–10 mg oral once daily. Unlike bosentan, ambrisentan has a low potential for drug interactions.[14]

Macitentan is a new potent nonpeptide nonselective ERA with a 50-fold higher affinity for ET_A than for ET_B receptors. Dose is 10 mg oral.[14]

Side effects of ERA are related to vasodilator properties such as headache, peripheral edema, nasal congestion, flushing, elevation in hepatic enzymes, peripheral edema, anemia, teratotoxicity, and male infertility.[13]

Newer Drugs

Riociguat is a new class of soluble guanylate cyclase stimulator. Guanylate cyclase is the intracellular receptor for NO, which has vasodilatory and antiproliferative effects on blood vessels, including the pulmonary arteries.

Recent PATENT 1 trial demonstrated improved exercise tolerance, hemodynamic parameters, and secondary outcomes with riociguat in people with PAH compared to placebo.[15]

Selexipag, an oral selective prostacyclin receptor agonist, has improved pharmacological properties and minimizes side effects associated with prostacyclin use. The dosing flexibility afforded by oral selexipag may facilitate achieving the maximum therapeutic effect with acceptable tolerability in patients with PAH.[16]

Surgical Risk

PH is an independent predictor of increased morbidity and mortality (4%–24%) following surgery, and these patients are high-risk candidates depending on severity of disease and surgical procedure.[9]

The assessment of perioperative risk depends on the type of surgery, the severity of PH, and the functional status of the patient. The outcomes of major surgeries showed mortality and short-term morbidity rates of 7% and 42%, respectively. Perioperative risk factors which increase morbidity and mortality include New York Heart Association (NYHA) grade >2, 6-min walk distance <300 m, history of computer-aided diagnosis, pulmonary embolism apart from emergency nature of surgery, anesthesia duration exceeding 3 h, and use of vasopressors.[17]

Preoperative Assessment

The preoperative evaluation of these patients includes assessment of functional state, severity of the disease, and type of surgery proposed. A detailed history of symptoms including dyspnea, chest pain, fatigue, and syncope should be elicited. NYHA functional class predicts survival in these patients. Severity of disease is also suggested by symptoms of low cardiac output, including metabolic acidosis, hypoxia, and syncope which is a poor prognostic sign.[9]

The 6-min walking distance is used to assess exercise capacity, and a reduced total distance is associated with a higher mortality.[18]

Preoperative investigations include routine blood tests, chest radiography, electrocardiography, echocardiography, pulmonary function tests (PFTs) including blood gas analysis, and right heart catheterization. Pro-brain natriuretic peptide level is an independent predictor for postoperative cardiac mortality in patients undergoing noncardiac surgery.[19] Echocardiographic predictors of poor prognosis include right atrial enlargement surface >27 mm^2, reduced tricuspid annular plane systolic excursion, and pericardial effusion.[20] Echo also evaluates biventricular function, valvular structures, and any intracardiac shunts. However, mPAP is often underestimated on echo; therefore, right heart catheterization is preferred. It allows differentiation between pre- and post-capillary PH in addition to determining pulmonary vascular reactivity to vasodilators. ECG is done to evaluate signs of RV strain or ischemia. PFT becomes useful in Group 3 subset while spirometry provides important information for estimating the severity and progression of the disease.[2] PH medications including calcium channel blockers, digoxin, diuretics, prostaglandin infusion, and sildenafil should be continued till the day of surgery. Warfarin should be bridged to low molecular weight/unfractionated heparin before surgery.

Monitoring

In addition to standard American Society of Anesthesiologists monitoring, invasive arterial blood pressure is required as hemodynamics can deteriorate rapidly in these patients. Temperature monitoring is must as hypothermia exaggerates PVR.[21] Pulmonary artery pressure monitoring with either pulmonary artery catheterization (PAC) or transesophageal echocardiography (TEE) helps in guiding anesthetic management, particularly in high-risk procedures. However, placement of PAC may result in transient ventricular arrhythmias that can compromise RV filling. PA rupture[22,23] is also more likely to occur in these patients, and the risks and benefits of this monitoring tool must be carefully weighed. TEE provides information about ventricular filling using left ventricular end-diastolic area in the transgastric short-axis view (normal values: 5.5-11.9 cm^2/m^2), pulmonary artery systolic pressure,

tricuspid regurgitation and cardiac output estimation using continuous Doppler methods. It also helps in earliest detection of ventricular ischemia by identifying regional wall motion abnormalities.[24] TEE helps in optimization of intraoperative fluid therapy as well, and caused a significant change in therapeutic management in about 30% of patients.[25] It has the potential to offer a noninvasive, valid alternative to Swan–Ganz catheters in the hemodynamic assessment of patients in the perioperative period.[26] Central venous oxygen saturation monitoring can be used as a marker of global tissue perfusion.

Choice of Anesthesia Technique

General anesthesia is preferred for all cardiac surgery patients in view of smooth induction and maintenance although few anesthesiologists prefer to administer regional anesthesia in selected cases.[27]

All standard anesthesia techniques can be used in these patients.[28] Advantages of regional anesthesia include maintenance of spontaneous breathing; thus avoiding elevation of pulmonary pressures, which is induced by mechanical ventilation.[29] Thoracic epidural anesthesia does not have any significant influence on oxygenation and PVR.[27] However, caution must be taken with regional anesthesia in patients with advanced stages of PH who cannot be subjected to the supine position for longer period of time. Furthermore, these patients receive anticoagulant medications and it should be given a due consideration.

General anesthesia with endotracheal intubation ensures adequate oxygenation and controlled ventilation, apart from the ability to administer selective pulmonary vasodilators. Nevertheless, anesthesia administration (including induction, maintenance, and emergence) may expose patients to physiological insults such as periods of apnea and hypoventilation, hypoxemia, fluctuations in body temperature, episodes of systemic hypotension, bursts of intense sympathetic stimulation arising from the unconscious experience of somatic pain, rapid fluid shifts and changes in cardiac preload, and mechanical ventilation.[30]

In addition, reduction in mean arterial pressure due to anesthetic agents-induced systemic vasodilation and positive pressure ventilation-induced elevation in PVR reduces coronary perfusion pressure to the right ventricle.[1]

All standard IV induction agents can be used in combination with opioids, as they did not influence PVR and oxygenation.[31,32] Histamine-releasing relaxants (atracurium) should be avoided, as they may further increase pulmonary resistance.[1] Volatile anesthetic agents up to 1 minimum alveolar concentration can be given safely without any negative effect on pulmonary vasculature.[33,34]

Authors prefer inhalational induction with sevoflurane in pediatric patients while combination of intravenous and inhalational induction for other patients.

Perioperative Management

Anesthetic management is aimed to prevent PH crisis and subsequent RV failure and is summarized in Table 4.

Recently, Pilkington *et al*. in their review postulated perioperative hemodynamic goals as to keep systolic blood pressure >90, mean arterial pressure >65 mmHg, mPAP <35, PVR/systemic vascular resistance ratio <0.5, and cardiac index >2.2 l/min/m^2.

Management of a pulmonary hypertensive crisis is based on general principles of avoiding factors which further increases PVR and simultaneously maintain RV perfusion too.[35]

General principles

- Avoid hypoxic pulmonary vasoconstriction, hypercarbia, acidosis, hypothermia, and high airway pressures
- Reduce RV afterload
- Maintain coronary blood flow and sinus rhythm.

Maintain cardiac output using

- Vasopressors – noradrenaline; vasopressin
- Inotropes – adrenaline; dobutamine
- Inodilators – milrinone; enoximone
- Intravenous vasodilators (caution if low systolic blood pressure)
  - Milrinone (25–50 mcg/kg bolus, followed by 0.5–0.75 mcg/kg/min continuous infusion) prostacyclin (4–10 ng/kg/min continuous infusion)
  - Iloprost (1–3 ng/kg/min continuous infusion)
  - Sildenafil (oral - 0.25–0.5 mg/kg every 4–8 h IV - 1.6 mg/kg/day)[36]
- Dobutamine: 2–5 μg/kg/min continuously
- Nitroglycerine: 2–10 μg/kg/min continuously
- Sodium nitroprusside: 0.2–0.3 μg/kg/min continuously

Table 4: Anesthetic and hemodynamic goals for pulmonary hypertension

Avoid escalation in PVR: Prevent hypoxemia, hypercarbia, acidosis and pain. Provide supplemental oxygen at all times

Keep higher inspiratory FiO$_2$ (titrate to 60%-100%)

PaCO$_2$ 30-35 mmHg

Low-tidal-volume ventilation to avoid overinflation of alveoli (goal: 6-8 ml/kg ideal body weight)

Maintain body temperature 36°C-37°C

Maintain SVR: Decreased SVR dramatically reduces CO due to "fixed" PVR

Avoid myocardial depressants

Maintain preload

Maintain sinus rhythm

PVR: Pulmonary vascular resistance, SVR: Systemic vascular resistance, CO: Cardiac output

Selective pulmonary vasodilators

- Iloprost (5–10 mg diluted in 10 ml saline, nebulized over 10 min, repeated every 2–4 h)
- Prostacyclin (25–50 mcg diluted in 50 ml saline, nebulized over 15 min, repeated every hour)
- NO (5–40 ppm continuously)
- Inhaled milrinone (2–5 mg) for 10–15 min (diluted in 10–15 ml of 0.9% NaCl)
- Inhaled epoprostenol (continuous) 10–50 ng/kg/min.

Postoperative Management

Patients with PH have risk of developing pulmonary vasoconstriction, arrhythmias, pulmonary thromboembolism, and RV failure in the postoperative period and should be fully monitored in the intensive care unit. Systemic pressure should be maintained with judicious use of vasopressors and inotropes, along with replacement of blood volume if needed.

Adequate analgesia is provided with regional blocks and nonopioid medications. Arrhythmias should be treated with amiodarone as beta-blockers are poorly tolerated in these patients. In patients in whom sinus rhythm cannot be restored, digoxin should be considered for rate control. Vasodilator therapies must be continued and gradually switched over to preoperative regimen.[37]

Pregnancy and Pulmonary Hypertension

Conventionally, pregnancy is to be avoided in severe PH and Eisenmenger syndrome. Recent systematic review revealed mortality rate around 17% in idiopathic PAH and 33% in PH associated with other conditions.[38]

Regarding medical management, ERAs are contraindicated during pregnancy due to their teratogenic effect, but epoprostenol, treprostinil, nebulized iloprost, sildenafil, and inhaled nitric oxide can be used.[39]

In general, elective cesarean section is preferred for delivery. However, maternal mortality is similar with both regional as well as general anesthesia (~20%).[40,41] The majority of deaths in pregnant patients with PAH occur in the peripartum period, mainly due to right heart failure and pulmonary thromboembolism.

Conclusion

PH and cardiac surgery are associated with significant morbidity and mortality and a reduction in quality of life. However, perioperative management has become more effective due to deeper understanding of the disease and newer therapeutic interventions. Advanced monitoring in the form of intraoperative TEE to assess biventricular dimensions and contractility, greatly facilitates the conduct of anesthesia. Nevertheless, selective pulmonary vasodilation by inhalation modality should be available intraoperatively, in addition to invasive hemodynamic

monitoring. Continuous postoperative monitoring and adequate analgesia should be taken care of. Successful perioperative management of such patients requires a thorough assessment, careful planning, and multispecialty involvement of anesthesiologist, surgeon, cardiologists, and pulmonologists, which allow for the best possible outcomes.

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Conflicts of interest

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